REMARKS

Claims 1-4, 6, and 9-27 are pending in this application. Claims 5, 7, and 8 have been canceled without prejudice. Applicant reserves the right to file a continuing application directed to these claims. Subject matter from claim 5 has been incorporated into claim 1 and into claim 10, and claim 6 has been amended to be in independent form including all of the limitations of the base claim and any intervening claims. New claims 21-27 have been added to the application. Support for claims 21, 23, 25, and 27 is found at claim 5. Support for claims 22, 24, and 26 is found at claim 6. No new matter has been added to the application by virtue of these amendments.

Rejection Under 35 U.S.C. § 102

Claims 1-5, 7-11, and 16 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Diancourt et al.

To sustain a rejection under § 102 the Patent and Trademark Office must abide by the following statement of the law:

> Under 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1554, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). In addition, the prior art reference must be enabling, thus placing the allegedly disclosed matter in the possession of the public. *In re Brown*, 329 F.2d 1006, 1011, 141 USPQ 245, 249 (CCPA 1964).

Akzo N.V. v. U.S. Int'l Trade Comm'n, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986).

Diancourt discloses a heparin-cholic acid conjugate (CHOHEP) and a heparin-stearic acid conjugate (STEHEP).

Claims 1 and 10 have been amended herein by deleting the terms "bile acids" and "alkanoic acids" and by incorporating subject matter from claim 5. Please note that "cholic acid" has not been incorporated into either claim 1 or claim 10. Diancourt fails to disclose each and every element of the presently claimed invention as amended.

It is respectfully submitted that in view of the amendments to claims 1 and 10 presented herein, the rejection of claims under 35 U.S.C. § 102(b) as allegedly anticipated by Diancourt is obviated. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 10-20 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Diancourt in view of Casey. Also, claims 10-14 and 17-20 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Diancourt in view of Patnaik.

Before discussing the rejections based on 35 U.S.C. § 103, it is thought proper to briefly state what is required to sustain such a rejection. "The PTO has the burden under section 103 to establish a *prima facie* case of obviousness." *In re Fine*, 837 F.2d

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1071, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In establishing a *prima facie* case of obviousness, the PTO "cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *Id.* at 1600. Rather, "[t]he test is whether the claimed invention as a whole, in light of all the teachings of the references in their entireties, would have been obvious to one of ordinary skill in the art at the time the invention was made." *Connell v. Sears, Roebuck & Co.*, 220 USPQ 193, 199 (Fed. Cir. 1983).

An excellent summary of how the prior art must be considered to make a case of *prima facie* obviousness is contained in *In re Ehrreich*, 200 U.S.P.Q. 504, 509-11 (C.C.P.A. 1979). There the court stated that a reference must not be considered in a vacuum, but against the background of the other references of record. It is stated that the question of a § 103 case is what the reference(s) would "collectively suggest" to one of ordinary skill in the art. However, the court specifically cautioned that the Examiner must consider the entirety of the disclosures made by the references and avoid combining them indiscriminately.

In finding that the "subject matter as a whole" would not have been obvious in *Ehrreich* the court concluded:

> Thus, we are directed to no combination of prior art references which would have rendered the claimed subject matter as a whole obvious to one of ordinary skill in the art at the time the invention was made. The PTO has not shown the existence of all the claimed limitations in the prior art or a suggestion leading to their combination in

the manner claimed by applicants.

To establish a case of *prima facie* obviousness by combining references, the prior art must provide some reason or motivation to make the claimed combination, *In re Dillon*, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990) (en banc). As more recently and aptly stated in *In re Jones*, 21 U.S.P.Q.2d 1941, 1943-44 (Fed. Cir. 1992) (emphasis in original):

> Before the PTO may combine the disclosure of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. . . . Conspicuously missing from this record is any *evidence*, other than the PTO's speculation (if it be called evidence) that one of ordinary skill in the . . . art would have been motivated to make the modifications of the prior art necessary to arrive at the claimed [invention].

Claim 10 as amended is drawn to a pharmaceutical composition comprising (a) a pharmaceutically effective amount of a composition of matter comprising a polysaccharide covalently bonded to a hydrophobic agent selected from sterols and certain specified bile acids and (b) a pharmaceutically acceptable carrier. Claims 11-15 are directed to the pharmaceutical composition of claim 10 wherein the pharmaceutically acceptable carrier is an oral drug carrier, a sustained release carrier, a polymeric matrix, and certain specified polymeric matrices, respectively. Claim 16 specifies that the polysaccharide is heparin.

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Claim 17 is drawn to a method of inhibiting blood coagulation on a medical device that comes in contact with blood comprising coating the medical device with a pharmaceutical composition comprising a polymeric matrix intimately admixed with a composition of matter comprising heparin covalently bonded to a hydrophobic agent. Claims 18 and 19 relate to the method of claim 17, further specifying the hydrophobic agent, and claim 20 further specifies the polymeric matrix.

Diancourt discloses a heparin-cholic acid conjugate (CHOHEP) and a heparin-stearic acid conjugate (STEHEP). Diancourt further discloses that CHOHEP forms 290 nm nanoparticles in aqueous solution and that a conjugate of dodecanal and heparin (DODHEP) was injected into rabbits as a dispersion in water.

Casey teaches the use of biodegradable copolymers for use as sutures and suture coatings. Casey also teaches that the properties needed for polymers to be used as sutures and suture coatings are biodegradability, biocompatibility, thermoplasticity, improved tie-down performance, and lubricity. Casey discloses the following with respect to poly(caprolactone)-poly(ethylene oxide)-poly(caprolactone) copolymers, at column 1, lines 6-25:

> As early as 1972, R. Perret and A. Skoulious, Makromol. Chem. 156, 143-156 (1972); Makromol. Chem. 162, 147-162 (1972); and Makromol. Chem. 162, 163-177 (1972) disclosed the synthesis and characterization of thermoplastic poly(caprolactone)-poly(ethylene oxide)-poly(caprolactone) (PCL-PEO-PCL) ABA triblock copolymers. The purification and crystallization behavior of these materials was extensively discussed. However, no mention

> was made as to the biodegradability of these polymers, their swelling behavior, or to any medical use such as suture materials or as suture coatings. Pitt and Schindler, U.S. Pat. No. 4,379,138 have published extensively on the biodegradability of PCL; therefore, the PCL-PEO-PCL triblock polymers should make attractive biodegradable hydrogel materials but this use was never mentioned.

Casey went on to discuss other copolymers that had been disclosed in the prior art as materials for sutures and suture coatings. At column 2, lines 8-14, Casey criticized the known copolymers (including PCL-PEO-PCL) and touted the advantages of Casey's new copolymers as follows:

> Conventional hydrogels which are made by crosslinking water soluble polymers have several drawbacks which are associated with their crosslinked nature. These include a lack of both solubility and processability. In contrast the block copolymers of this invention are thermoplastic. They are soluble in common organic solvents and are fusible.

Patnaik discloses bioactive polymer coatings, more particularly, bioactive polymer coatings where bioactive molecules are attached to polyurethane backbones via amine-terminated spacers. An example of such a bioactive polymer coating consists of a polyesterurethaneurea as a polymer backbone, poly(ethylene oxide) as the spacer, and heparin as the bioactive agent.

The Examiner justified rejection of claims 10-20 in view of the combination of Diancourt and Casey as follows:

> It would have been obvious for a person of ordinary skill in the art at the time of the invention to substitute a hydrogel such as a poly((ethylene oxide)-poly(ε-caprolactone)) copolymer as taught by CASEY for the carrier of DIANCOURT. An ordinarily skilled worker would

> have been motivated to do so, with a reasonable expectation of success, because CASEY had suggested the utility of such carriers as biodegradable hydrogel materials, and that the [*sic*] could be used as coatings for sutures.

With respect to claims 10-16, neither Diancourt nor Casey discloses or suggests the pharmaceutical compositions of these claims. Diancourt fails to disclose or suggest the polysaccharide-sterol or polysaccharide-bile acid conjugates as claimed. Casey acknowledged the existence of poly(ethylene oxide)-poly(caprolactone) copolymers, but denied knowing any medical use for such copolymers. Nothing in the combination of Diancourt and Casey discloses or suggests a pharmaceutical composition comprising the hydrophobized heparins of the present invention and a sustained release carrier, such as a polymeric matrix in general or the specifically named polymeric matrices, including poly(ethylene oxide)-poly(caprolactone), in particular. The Examiner concluded that it would be obvious to substitute the poly(ethylene oxide)-poly(caprolactone) polymer mentioned as an inferior hydrogel for a suture material or a suture coating by Casey for the water carrier mentioned by Diancourt. Applicants respectfully submit that nothing in the prior art would lead a person of ordinary skill in the art to make the combination of Diancourt and Casey. Moreover, even if a person of ordinary skill in the art did combine Diancourt and Casey, there is nothing in these references to lead such person to make the presently claimed invention.

With respect to claims 17-20, nothing in the combination of Diancourt and Casey would lead a person of ordinary skill in the art to a method of inhibiting blood coagulation on a medical device by coating such medical device with an admixture of hydrophobized heparin and a polymeric matrix. As stated above, Diancourt fails to disclose or suggest the polysaccharide-sterol or polysaccharide-bile acid conjugates as claimed, and Casey fails to disclose admixing such polysaccharide-sterol or polysaccharide-bile acid conjugates with a polymeric matrix, and then coating a medical device with such admixture for inhibiting blood coagulation.

Therefore, the combination of Diancourt and Casey fails to show the existence of all the claimed limitations in the prior art or a suggestion leading to their combination in the manner claimed by applicants. In other words, a person of ordinary skill in the art cannot arrive at the presently claimed invention having Diancourt and Casey before him or her. Further, even if a person of ordinary skill in the art could arrive at the presently claimed invention from a combination of Diancourt and Casey, there is no motivation in the cited art to make such a combination. Without such a motivation in the prior art for making the combination of references, it appears that the Examiner has impermissibly slipped into using hindsight for reconstructing the presently claimed invention after having read the specification for a guide. This use of hindsight is not permitted in making a decision on

patentability under Section 103. Were it not for having first read Applicants' disclosure and then by hindsight application attempting to weave together the references, there is no reasonable way that the cited references would have been collectively considered. As the court stated in *In re Carroll*, 202 U.S.P.Q. 571, 572 (C.C.P.A. 1979):

> One of the more difficult aspects of resolving questions of non-obviousness is the necessity "to guard against slipping into use of hindsight." Graham v. John Deere Co., 383 U.S. 1, 36, 148 USPQ 459, 474 (1965). Many inventions may seem obvious to everyone after they have been made. However, 35 USC 103 instructs us to inquire into whether the claimed invention "would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." Thus, in deciding the issue of obviousness, we must look at the prior art presented from a vantage point in time prior to when the invention was made, and through the eyes of a hypothetical person of ordinary skill in the art.

Applicants respectfully submit that if one follows the above guidelines and analyzes the art properly, then there is no suggestion of the invention as claimed.

Turning now to the rejection of claims 10-14 and 17-20 over the combination of Diancourt and Patnaik, neither Diancourt nor Patnaik individually nor both references combined disclose or suggest the presently claimed invention. Neither reference discloses or suggests the hydrophobized heparins as claimed. Neither reference discloses or suggests mixing the hydrophobized heparin with a sustained release carrier or polymeric matrix. Moreover, neither reference discloses or suggests coating a medical

device with an admixture of a hydrophobized heparin and a polymeric matrix.

Therefore, the cited references fail to show all of the claimed limitations in the prior art or a suggestion leading to their combination in the manner claimed. Further, there is no suggestion or motivation in the prior art for making the combination of these two references. Thus, even if the references did contain the disclosures needed to properly reject the claimed invention, there is no reason, absent hindsight, to make the combination of references.

For these reasons, it is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the presently claimed invention. Therefore, withdrawal of the rejections under Section 103 is respectfully requested.

Another aspect of the claimed invention that is highly relevant to the issue of nonobviousness is consideration of the so-called secondary considerations or objective indicia of nonobviousness. *Graham v. John Deere Co.*, 148 U.S.P.Q. 454 (U.S. 1966). These objective indicia must <u>always</u> be considered along with the factual inquiries of scope and content of the prior art, differences between the prior art and the claimed invention, and the level of skill of one of ordinary skill in the art, and are often the most probative and cogent evidence on the issue.

Stratoflex Inc. v. Aeroquip Corp., 218 U.S.P.Q. 871, 879 (Fed. Cir. 1987). Applicants present evidence of unexpected or surprising results obtained with one of the presently claimed compositions. This evidence is presented as further demonstration that a *prima facie* case of obviousness is lacking in the present case, and in no way is the presentation of such evidence to be construed as an admission that a *prima facie* case of obviousness has been established.

Applicants herewith present a Declaration Under 37 C.F.R. § 132 by Dr. Youngro Byun, one of the applicants. Dr. Byun conducted a comparative test of two hydrophobized heparin conjugates according to the present invention versus a heparin-cholic acid conjugate, such as is disclosed by Diancourt. Oral absorption of the heparin-deoxycholic acid conjugate (heparin-DOCA) and the heparin-cholesterol conjugate were shown to be unexpectedly and surprisingly better than the oral absorption of the heparin-cholic acid conjugate. For this additional reason, it is respectfully submitted that the heparin-DOCA composition is unobvious over the prior art, and withdrawal of rejections under Section 103 is respectfully requested.

Conclusion

Should the Examiner deem it advisable to conduct a telephone interview for any reason, the undersigned attorney would be most

agreeable to receiving a telephone call to expedite the prosecution of the application.

For the reasons given above, Applicant respectfully requests reconsideration and allowance of claims 1-4, 6, and 9-27 and passage of this application to issue.

Dated this 15th day of November, 2000.

Respectfully submitted,

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